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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,772	PETIT ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-6 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to Paper No. 24, filed on April 23, 2003. Claims 3-6 and 8-10 are pending. This action is made FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3-6 and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3-6 and 8-10 because it is not clear as to what is encompassed by "arterial complications". There is no fixed definition in the art for "arterial complications"; and it is not clear as to whether the method is one in which the ketolide directly effects "arterial complication" or if the ketolide may act to prevent any process which leads to "arterial complication". Furthermore, it is not clear as to how one can prevent arterial complications when they already have arterial complications. That is, the claims are drawn to a method of ***preventing*** arterial complications, however, the first step involves selecting a patient ***with*** arterial complications.

Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 3-6 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the

constitute adequate enablement".

Also, MPEP 2164.01 states:

"Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)."

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation:

"They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) The quantity of experimentation necessary

In order to practice the invention, the skilled practitioner must perform an experiment on an individual who has ***any*** "arterial complications", administer the compounds of the present invention and then monitor the individuals for a long period of time to determine whether they developed or did not develop the above complications. In fact, the recitation of "preventing" denotes that once the ketolides are administered to a patient, said patient will never suffer from arterial complications. This would require the practitioner to monitor said patient for many years.

On page 6, lines 24-27, the specification discusses that "arterial complications" include cerebrovascular accidents, myocardial infarction, unstable angina following atherosclerosis, and any other complications (e.g., angioplasty, endoarterectomy, stent placement, etc.), which can be considered as "arterial complications".

Therefore, the claims can be interpreted as being drawn to methods of preventing, for example, myocardial infarction. This involves, at least, the screening individuals who are likely

to develop the above complications or any other complications, which can be considered to be "arterial complications". This may involve a thorough analysis of a person's medical history, as well as, blood and/or genetic analysis to eventually lead a practitioner to determine whether someone is likely to develop "arterial complications". Additionally, this involves, first, identifying possible symptoms of what constitutes an individual who is likely of developing the above complications, as well as, a standard for determining whether the complications are "prevented". Also, the screening of individuals who might be likely to develop the above complications must be tested against a control group who may not be likely to develop said complications. Clearly, even the possible experiment to perform the claimed method involves an extremely high level of experimentation (which is not taught in the specification), let alone, its high degree of unpredictability. In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Therefore, the quantity of experimentation is not only difficult, but also unpredictable.

(2) The amount of direction or guidance presented

The specification (pg. 9) provides guidance on a method of an in vitro platelet aggregation test. This Example demonstrates the comparison of a "product P", aspirin and platelet aggregation, from blood taken from rabbits. The specification (pg. 9) also states, "P_1, P_2 and P_3 ...also show 'good activity' on this in vitro platelet aggregation test".

While the specification may provide guidance for carrying out the steps of an in vitro platelet aggregation test, the specification provides no evidence that compounds of the invention are associated with "preventing arterial complications in a patient". While one of ordinary skill in the art can carry out the method steps an in vitro platelet aggregation test, the specification provides no guidance that performing said method steps will result in the desired outcome of the claimed method, namely, ***preventing any*** "arterial complication" in a patient. It is also noted that the specification provides no standard for determining when a patient is considered as having "arterial complications". That is, the specification does not provide any guidance as to whom this administration of ketolides is intended for. In effect, it seems clear that every patient would want to prevent "arterial complications".

Applicants, at best, have taught that P- P_3 shows "good activity" in an in vitro platelet aggregation test. However, the specification provides no specificity as to how to carry out the claimed invention or that ketolides actually accomplish what the claimed methods sets forth. Therefore, one of ordinary skill in the art cannot interpret the teachings of the specification to arrive at the claimed methods.

(3) The presence or absence of working examples

One working example (pg. 9) is presented which provides guidance on a method of an in vitro platelet aggregation test. This Example demonstrates the comparison of a "product P", aspirin and platelet aggregation, from blood taken from rabbits. The specification (pg. 9) also states, "P_1, P_2 and P_3 ...also show 'good activity' on this in vitro platelet aggregation test". However, there are no examples or relevant teachings demonstrating the prevention of ***any*** arterial complications in a patient.

(4) The nature of the invention

The invention is broadly directed to a method of ***preventing any*** arterial complication in a patient. Thus, the nature of the invention pertains to prevention of disease.

(5) The state of the art

The prior art demonstrates not only the high quantity of experimentation needed to carry out a method for "preventing" arterial complications (e.g., arterial complications associated with atherosclerosis), but also teaches the unpredictability of carrying out such a method.

Hiatt, W. R. teaches (J Intern Med (2002) 251(3): 193-206) the use of antiplatelet therapy for preventing atherothrombotic events in peripheral arterial disease. Specifically, Hiatt teaches studies determining the utility of antiplatelet therapy in preventing "arterial thrombotic complications associated with atherosclerosis" involve using many test subjects over a significant period of time (see Table 3, pg. 199). Even after such extensive trials, for example, "clinical trials have failed to demonstrate the anti-thrombotic efficacy of dipyridamole as monotherapy [80]. Dipyridamole and aspirin as combination therapy has been evaluated in several clinical trials with inconsistent results." (pg. 201, 2nd column). Finally, Hiatt teaches:

> Studies evaluating the early initiation of antiplatelet therapy in high-risk patients, PAD undergoing endovascular procedure will help define the role of these agents in the management of patients with PAD.

(pg. 203, 1st column)

Kullo et al. (MAYO Clinic Proceedings (2000) 75(4): 369-80) teaches while

> Spontaneous platelet aggregation was a useful marker for survival and secondary coronary events among a cohort of patients *followed up for 5 years*...diverse measurements of platelet function...are technically difficult to perform. Physicians must

> distinguish between spontaneous platelet aggregation, which is induced by circulating agonists in the blood, and the response of platelets to agonists added externally.

(pg. 372)

Drouet, L. (Cerebrovasc Dis (2002) 13 Suppl 1: 1-6) teaches :

> "Antiplatelet therapy should also be considered in high-risk patients without a history of atherothrombotic events or current symptoms and in those with subclinical manifestation of atherothrombosis; however, *data from clinical trials in such patients are not yet available*…Thus, *clinical trials that are designed to evaluate the ability of antiplatelet agents to prevent such downstream damage are warranted in the future.*" (pg. 5, 2nd column).

Therefore, the state of the art teaches the high quantity of experimentation needed to carry out a method for "preventing" arterial complications, but also teaches the unpredictability of carrying out such a method. The specification's teachings do not remedy this high quantity and unpredictable level of experimentation.

(6) The relative skill of those in the art

The level of skill in molecular biology is high, as one of ordinary skill in the art would have to experiment perform experiments in a population of individuals who are likely to develop "arterial complications", and determine whether the administration of the compounds of the

but also it would be very unpredictable (see above), as there is no indication that the compounds of the invention can be used to treat "arterial complications, let alone a higher standard of "preventing" said complications.

(7) The predictability or unpredictability of the art

The unpredictability of the art is demonstrated above. Specifically, the art teaches that more trials for "preventing arterial complications" (e.g., associated with atherosclerosis) are

needed, and that there has been mixed results in those trials using antiplatelet agents to date. Additionally, because the claims are directed to "preventing", and not, for example, to "treating", the standard of review for demonstrating "prevention", rather than treatment, is higher and more unpredictable, since the skilled artisan cannot be sure that a patient will never develop arterial complications, which is suggested by a claim is drawn to a method "preventing". However, for example, a method of treating does not ensure success, as does a method of preventing. Furthermore, even assuming the specification taught an assay, which demonstrated the prevention of a particular arterial complication, it is unpredictable as to whether the myriad of possible complications that are encompassed by "arterial complications" would also be prevented.

(8) The breadth of the claims

The invention is directed to a method of ***preventing any*** arterial complications in a patient with ***any*** arterial complications by administering an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts sufficient to prevent said complications.

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification as to any correlation of the prevention of "arterial complications" in a patient by administering the compounds of the invention, undue experimentation would be required to practice the invention as it is claimed.

Response to Applicant's Arguments

Applicants argue the method of preventing arterial complications is fully supported on

page 6 of the application and by the test data set forth in the application with the four preferred products (see page 2 of Applicant's response of April 2nd, 2003).

However, as discussed above, the specification teaches a single example in rabbits, wherein products P_1, P_2 and P_3 show "good activity" in a vitro platelet aggregation test. However, there are no examples or relevant teachings demonstrating the prevention of ***any*** arterial complications in a patient. Furthermore, the art demonstrates the unpredictability of using antiplatelet testing and therapy for treatment of arterial complications, especially those associated with atherosclerosis (see above). Additionally, because the claims are directed to "preventing", and not, for example, to "treating", the standard of review for demonstrating "prevention", rather than treatment, is higher and more unpredictable, since the skilled artisan cannot be sure that a patient will never develop arterial complications, which is suggested by a claim is drawn to a method "preventing". Accordingly, given the lack of guidance in the specification and the art as outlined above, the trial and error analysis that the skilled artisan would have to perform to practice the invention as broadly as it is claimed is unpredictable, thus constituting undue experimentation.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 3-6 and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Agouridas et al. (USPN 5,747,467).

Due to the indefinite and broadly claimed language of "arterial complications", claims 3-6 and 8-10 have been interpreted as encompassing methods for the prevention of ***any*** "arterial complication" by selecting ***any*** patient with ***any*** "arterial complication", and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts.

Agouridas et al. teaches a method of preventing bacterial infections in warm-blooded animals including humans comprising, administering to warm-blooded animals an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts (col. 5, ln. 33-38). Specifically, Agouridas teaches the administration of ketolides is effective in treating septicemia, acute anginas and other "arterial complications" (see col. 5). Therefore, Agouridas teaches the prevention of "arterial complications" by administrating an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts. With respect to claims 3-6 and 8-9, the reference teaches a plurality of specific ketolides that can be used in the method in this method of treating warm-blooded animals (see whole document). With respect to claim 10, the reference teaches that the usual daily dose is 1.5 to 6 mg/kg, and therefore, provides a range equivalent to the range provided in claim 10. For example, if the daily dose was at 4mg/kg, and an individual to whom the ketolide was administered weighed 100 kg, then 400 mg would be administered to said individual per day.

Response to Applicant's Arguments

Applicants argue Agouridas "is directed to methods of treating bacterial infections and this is an entirely different type of patient. Therefore, Agouridas et al. does not anticipate or render obvious the application, since the patient being treated is entirely different and the activity is due to the anti-platelet aggregating activity..." (pg. 3 of Applicants' response).

Applicants' arguments have been considered, but are not persuasive for the following reasons. First, the claims do not recite or require the properties of anti-platelet activity. Additionally, due to the indefiniteness and broadly claimed language of "arterial complications", the claims have been interpreted as encompassing methods for the prevention of ***any*** "arterial complication" by selecting ***any*** patient with ***any*** "arterial complication", and administering to said patient an effective amount of a ketolide or its non-toxic, pharmaceutically acceptable acid addition salts. Given the broadest reasonable interpretation, complications such as septicemia, acute anginas, for example, are considered to be encompassed by the recitation of "arterial complication". Accordingly, because Agouridas teaches the prevention of "arterial complications", the rejection is maintained.

Conclusion

8. No claims are allowable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (703) 308-2199. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax numbers for the organization where this application or proceeding is assigned are (703) 308-4556 and (703) 308-4242. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
July 15, 2003

CARLA J. MYERS
PRIMARY EXAMINER